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Appl. No. 10/052,889
Ammdt. dated July 31, 2006
Amendment under 37 CFR 1.116 Expedited Procedure
Examining Group 3738

JUL 31 2006

REMARKS**I. Status of the Claims**

Originally filed claims 1-23 have been canceled. Later added claims 24-28 are currently under examination.

II. Supplemental Declaration

A supplemental declaration under 37 C.F.R. §1.132 is filed along with the present response to the Final Office Action mailed March 6, 2006. Under 37 C.F.R. §1.116(e), the consideration of additional evidence requires a showing of good and sufficient reasons why the evidence is necessary and why it was not earlier presented. The additional evidence consisting of a Rule 132 declaration is necessary because the Examiner has, in the Final Office Action, challenged the credibility of the earlier Rule 132 declaration by the declarant, which was filed with Applicants' last response. The evidence being presented in this supplemental declaration does not present any new argument. It merely corroborates the factual positions presented earlier. This evidence was not presented earlier because, prior to the Examiner's raising his doubts about the specific issues the supplemental declaration seeks to address, Applicants did not believe there was the need to provide this particular evidence. It is hoped that the issues in dispute will be fully addressed or that the issues for appeal will be simplified after the Examiner has had an opportunity to review the additional evidence.

III. Claim Rejections**A. Double Patenting**

In the final Office Action mailed March 6, 2006, the rejection of claims 24-28 was sustained under the judicially created doctrine of obviousness-type of double patenting as allegedly being unpatentable over claims 1, 3, 4, 8, and 10 of U.S. Patent No. 6,371,992. Applicants will gladly consider filing a terminal disclaimer once all pending claims are found otherwise allowable.

Appl. No. 10/052,889
Amdt. dated July 31, 2006
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Examining Group 3738

PATENT

B. 35 U.S.C. §103

The Examiner sustained the rejection of claims 24-28 for alleged obviousness over Bishopric *et al.* (U.S. Patent No. 5,855,620) or Goldstein (U.S. Patent No. 5,632,778) in view of Gregory (U.S. Patent No. 5,990,379). Applicants respectfully traverse the rejection for reasons already presented in Applicants' previous responses.

No Prima Facie Obviousness Has Been Established

As previously stated, Applicants do not believe that the obviousness rejection is proper because the Examiner has not established a *prima facie* showing of obviousness. Specifically, by way of a Rule 132 declaration by the lead inventor Dr. Emil Tanagho (filed with Applicants' response of December 16, 2005), Applicants have established that, when viewed together, the cited references do not motivate or suggest to one of skill in the art to combine the teaching of these references, and that there is no reasonable expectation of success to arrive at the present invention by combining the teaching of the cited references. Even assuming *prima facie* obviousness were properly established, Applicants further contend that it would be sufficiently rebutted by Dr. Tanagho's declaration, as the declaration presents clinical evidence to demonstrate that the acellular matrix graft of the present invention has surprising and extraordinary properties, which simply cannot be expected from combined teaching of the cited references.

In the final Office Action of March 6, 2006, however, the Examiner sustained the rejection, arguing that the motivation to combine Gregory with the primary references stems from the general desire to replace damaged tissue with the same type in a patient. The Examiner also argued that the references all come from the same field of endeavor, one would therefore be motivated to use the method taught in the primary references to make ureter tissue graft (see the paragraph bridging pages 4 and 5 of the final Office Action). With regard to the expectation of success, the Examiner found Applicants' argument unpersuasive for failure to point out the differences in properties between the urethra/ureter tissues and that of the other tissues (see the first full paragraph on page 5 of the final Office Action).

Appl. No. 10/052,889
Amdt. dated July 31, 2006
Amendment under 37 CFR 1.116 Expedited Procedure
Examining Group 3738

PATENT

Applicants respectfully disagree. First, Applicants have previously argued and Dr. Tanagho has attested in his declaration that there is no motivation to combine the limitations of the claims of this application, because of the different purposes the methods in the art are intended for. On the other hand, the Examiner's assertion of a general desire in choosing the same type of tissue for making matrix graft finds no specific support in any of the three references and is therefore a motivation apparent only in the hindsight.

Second, as Applicants have previously argued and Dr. Tanagho has attested, even if there is motivation to combine Gregory with either one of the two primary references, there is no reasonable expectation of success, primarily due to the drastically different characteristics of various tissue types. The Examiner is incorrect to allege that Applicants have failed to point out the differences between the tissue used for preparing the claimed matrix of this invention, *i.e.*, urethra/ureter smooth muscles, and other tissue types such as those described in the Bishopric or Goldstein reference. Applicants have in fact offered this information. As an example, in paragraph 14 of Dr. Tanagho's declaration filed December 16, 2005, it is stated that, "[t]here is a large number of different types of tissues present in a human body, and that the tissues differ drastically in terms of strength, elasticity, and porosity of the cellular matrix. For instance, heart valves are a type of highly specialized tissue in that the tissue is nearly acellular except for a thin external layer of cells that can be readily removed by a variety of treatment methods to achieve a thick, dense, and relatively stiff matrix. In contrast, the intact matrix of smooth muscles such as that forms ureter or urethra provides a waterproof sheath with much higher flexibility." Thus, Applicants' contention should not be challenged on the basis of the alleged lack of discussion regarding the differences in different tissue types.

Applicants reiterate that because the cited references provide no suggestion or motivation to combine the claim limitations that might be found in the references, and there is certainly no reasonable expectation that such combination would produce a collagen/elastin matrix having the properties of flexibility, water impermeability, and susceptibility for muscle cell repopulation, no *prima facie* case of obviousness is established.

Appl. No. 10/052,889
Amdt. dated July 31, 2006
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Examining Group 3738

PATENT

Any Possible Prima Facie Obviousness Has Been Rebutted by Unexpected Results

Applicants also take the position that, even assuming that the Examiner has properly established a *prima facie* showing of obviousness, it has been effectively rebutted by the unexpected results described in Dr. Tanagho's declaration under 37 C.F.R. §1.132. In the final Office Action, the Examiner dismissed Dr. Tanagho's declaration regarding the unexpected properties of the claimed matrix graft, citing the following reasons: first, the declaration is merely the opinion of one inventor, no actual data are provided to compare the claimed matrix against the closest prior art. It is therefore not clear what kind of difference there would be (see the paragraph bridging pages 5 and 6 of the final Office Action); second, successful results on only one patient were provided, which had limited evidentiary value (see the first full paragraph on page 6); and third, no quantitative data is provided; only qualitative data was provided for one patient, and the data was not compared with test data on tissues of the closest prior art. The Examiner thus concluded that the declaration merely states an inventor's opinion and fails to provide objective proof of difference between the claimed invention and the prior art (see pages 4-5 of final Office Action).

In response, Applicants first contend that the Examiner cannot simply disregard a declarant's assertion of unexpected results merely because the declarant is one of the inventors or there is insufficient evidence on the record that supports the assertion. In the case of *In re Soni* (34 USPQ2d 1684, Fed. Cir. 1995), the claimed composition was rejected for obviousness. In the specification, the applicant showed improved properties of the composition over the art and asserted that such improvement amounted to unexpected results. The court reversed the rejection, stating that, "when an applicant demonstrates *substantially* improved results, ... and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of evidence to the contrary.*" *Soni*, at 1688, emphasis in original. In the present case, Applicants have indeed provided experimental evidence that the matrix graft they invented perform substantially better than any material known in the art prior to this invention, particularly in animal studies (see more detailed discussion in the paragraph below). Applicants have also asserted that the performance of the claimed matrix graft amounted to unexpected

Appl. No. 10/052,889
Amdt. dated July 31, 2006
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Examining Group 3738

PATENT

results, for example, in Dr. Tanagho's declaration filed December 16, 2005. Since the fact pattern of the present application is so closely in parallel with that of *Soni*, Applicants do not believe that the Examiner can properly dismiss the asserted unexpected results "*in the absence of* evidence to the contrary."

Secondly, Applicants contend that the unexpected properties of the claimed matrix graft described in Dr. Tanagho's declaration are not merely "a statement of one inventor's opinion" without any evidentiary support. To this end, a supplemental Rule 132 declaration by Dr. Tanagho has been submitted concurrently with this response to address the Examiner's attack on the declaration, namely, the Examiner's assertions of success in only one patient and lack of comparative or quantitative data demonstrating the unexpected properties of the claimed matrix graft of this invention. Regarding the successful repair of ureter/urethra in human patients, Dr. Tanagho attests,

Contrary to the Examiner's assertion, the present inventors have so far performed on at least 12 human patients surgical procedures similar to that described in my previous declaration using the claimed matrix graft of this invention. In each case, the procedure has led to dramatic improvement in patient's condition as indicated by x-ray imaging and urine flow rate measurement. Thus, the extraordinary properties and unexpected success of the claimed matrix graft are not merely my personal opinion; they are facts proven by a multitude of clinical studies. (paragraph 5 of the supplemental declaration)

Thirdly, Dr. Tanagho also explains in his supplemental declaration why it is not possible to provide data directly comparing the properties of the claimed graft of this invention and that of the matrix of the art:

In direct contrast with the matrix graft of this invention, which is derived from ureter or urethra smooth muscle tissue, the references by Bishopric and Goldstein teach the making of an acellular collagenous matrix derived from different tissue types, for example, heart valve and skin. The reference by Gregory teaches elastin extraction and purification, which leads to the disruption of the collagenous network of a tissue. For a graft material to be useful in ureter/urethra repair, the material must have

Appl. No. 10/052,889

PATENT

Arndt. dated July 31, 2006

Amendment under 37 CFR 1.116 Expedited Procedure

Examining Group 3738

a high level of structural integrity and flexibility, as well as water impermeability, such that the repaired tissue can perform its intended function, i.e., to hold urine under a certain amount of pressure. The material produced by Bishopric, Goldstein, or Gregory does not meet such requirements because of the chosen tissue type or the loss of collagen, as tissue graft derived from heart valve or skin does not have the required elasticity and tissue without an intact collagen network does not have the required strength and structural integrity. Thus, no person of skill in the art would ever consider using the material described in the references for implantation on a human patient to repair damaged ureter or urethra tissue. The type of comparative data the Examiner has asked for simply cannot be obtained for ethical reasons. (paragraph 6 of the supplemental declaration)

Dr. Tanagho disagrees with the Examiner that no quantitative data were presented in his earlier declaration by pointing out that results of several animal experiments quantitatively illustrating the outstanding, unexpected quality of the matrix of this invention can be found in the four references named in paragraph 15 of the previous declaration. He further explains, "[i]nsofar as the surgical repair of human ureter or urethra is concerned, quantitative data are not a preferred means to evaluate the effectiveness of the procedure. Because patient's overall physical condition (age, general health, etc.) as well as the extent and severity of tissue damage can vary significantly from individual to individual, quantitative data can provide only limited useful information. Moreover, surgical retrieval of post-implantation matrix graft is often necessary in order to obtain quantitative data for assessing the effectiveness of the matrix graft. Such retrieval, however, can be performed ethically in animals only and not in human patients."

See paragraph 6 of the supplemental declaration.

Because each of the Examiner's specific concerns pertaining to Dr. Tanagho's earlier declaration has been fully addressed, it is respectfully submitted that Applicants have properly established, by way of Dr. Tanagho's declarations, that the matrix graft of this invention has extraordinary properties and is surprisingly effective in its use for repair of ureter or urethra. These unexpected properties and results cannot be gleaned from the three cited references even when they are viewed together.

Appl. No. 10/052,889
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Examining Group 3738

PATENT

Accordingly, even if *prima facie* obviousness is established, it has been rebutted by Applicants. Thus, the withdrawal of the §103 rejection based on Bishopric *et al.* or Goldstein in light of Gregory is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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